A four-week, randomized, double-blind trial of the efficacy and safety of SKI306X, a herbal anti-arthritic agent versus diclofenac in osteoarthritis of the knee

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Running Title : Efficacy and safety of SKI306X

Numbers of pages and tables : 23 pages and 4 tables

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ABSTRACT

The efficacy and safety of SKI306X, a herbal anti-arthritic agent, was compared with that of diclofenac sodium for the treatment of osteoarthritis of the knee. In a randomized, double-blind, active comparator-controlled trial, a total of 249 patients were randomly assigned to receive either 200 mg of SKI306X three times daily or 100 mg of diclofenac sustained release (SR) once daily. Clinical efficacy variables (Visual Analog Scale, Lesquesne index, and global satisfaction score) and adverse events were monitored at baseline and 2nd and 4th weeks of treatment. SKI306X demonstrated efficacy statistically comparable to that of diclofenac, as assessed by the Visual Analog Scale and patients' and investigators' global satisfaction score. Both treatments were well tolerated, however, the SKI306X treatment group experienced less heartburn (4.0% vs. 13.7%, p=0.015, chi-square test). In this four-week trial, SKI306X was well tolerated and demonstrated clinical efficacy comparable to that of diclofenac SR.

Key words: osteoarthritis, SKI306X, diclofenac, anti-arthritis agent

INTRODUCTION

Osteoarthritis (OA) is the most common arthritic disease. The prevalence of OA increases with age and it may affect as many as 68% of patients over the age of 65 (Brandt KD *et al.*, 1991). Progressive pain, stiffness, limitation of motion, and deformity of the joints characterize the disease. The pharmacological treatment options currently available for OA focus mainly upon the control of pain and inflammation with analgesics and non-steroidal anti-inflammatory drugs (NSAIDs).

In spite of their proven effectiveness in pain relief and reduction of inflammation, NSAIDs may cause significant adverse effects, including gastrointestinal (GI) toxicity such as gastritis and ulcer, as well as renal toxicity (Fries JF, 1991; Murray M and Brater D, 1990). Moreover, NSAIDs do not alter the course of disease progression. A new class of NSAIDs, the selective cyclo-oxygenase type-II (COX-II) inhibitors, which were developed in order to reduce GI toxicity, was found to have clinical efficacy comparable to that of traditional NSAIDs (Lane NE, 1997; Vane JR and Botting RM, 1990). However, COX-II inhibitors still are only a symptomatic rather than a disease modifying treatment.

Given the high prevalence of OA and limited pharmacological management options, much effort has been directed toward developing a more effective and safer drug. In Far

East Asian countries, about 600 natural herbs have been used for the treatment of inflammatory conditions such as arthritis or lymphadenitis for many years. Among these 600 herbs of Oriental medicine, 53 species were selected and screened for their analgesic, anti-inflammatory, anti-collagenase, and anti-platelet activities in vitro and in animal studies. Based on the results of these screening tests, SKI306X was developed as a new herbal extract consisting of a mixture of Clematis Radix, Trichosanthes Root and Prunella Spike (Ahn JS *et al.*, 1996; Kim HT *et al.*,1996; Park KS *et al.*,1995). The results of preclinical studies demonstrated that SKI306X had significant anti-inflammatory and analgesic properties, improved microcirculation and prevented joint cartilage degeneration in animal models (Choi JH *et al.*, 2002). A previous double-blind, placebo-controlled study also confirmed the clinical efficacy and tolerability of SKI306X in patients with osteoarthritis of the knee (Jung YB *et al.*, 2001).

The main objective of this study was to compare the efficacy, safety and tolerability between SKI306X and diclofenac, an NSAID that is one of the leading drugs of its class for the treatment of degenerative joint disease (Amundsen *et al.*, 1983; Todd PA and Sorkin EM, 1998) by four-week, double-bind, double dummy, multicenter clinical trial.

MATERIALS AND METHODS

Subjects

Patients aged 35 to 75 years old were eligible to participate in the study if they fulfilled the American College of Rheumatology (ACR-20) diagnostic criteria of OA of the knee (Altman R *et al.*, 1986). These criteria included the presence of knee pain, radiographic evidence of osteophytes, and at least one of the followings: i) age older than 50 years, ii) morning stiffness lasting less than 30 minutes, and iii) crepitus with motion. Among those who met the diagnostic criteria, patients with at least moderate pain in the affected knee joint, i.e., the visual analogue scale (VAS) of higher than 35 mm (VAS ranges from 0 mm [no pain] to 100 mm [unbearable pain]) were enrolled in this study. Patients with the following conditions were excluded: i) history of liver or kidney disease; ii) abnormal values of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) or creatinine at the screening visit; iii) active infection requiring antibiotic treatment; iv) previous history of sensitivity to NSAIDs; v) treatment with corticosteroids, other NSAIDs, or antacid medication within 1 week prior to enrollment; or vi) childbearing potential, pregnancy, or lactation. All patients were required to have a one-week washout period from prior medications. Written informed consent was obtained from all patients before the entry into the study, which was performed according to the principles of the

Declaration of Helsinki and approved by the Institutional Review Boards for all investigational sites and the Korean FDA.

Study Design

Following the confirmation of eligibility, patients were randomized to receive either SKI306X 200 mg 3 times daily or diclofenac sustained release (SR) 100 mg once daily. We used stratified block randomization with stratification by study site using a block size of 4 or 6. The SAS program (version 6.12) was used for random number generation following uniform distribution. Blinding was maintained throughout the study period by using double-dummy technique; 1) assigned code was used strictly throughout the study after randomization, 2) both treatment groups were administered test drugs three times a day using placebo pills. SKI306X group was received SKI306X 200mg and diclofenac sustained release(SR) shaped placebo three times daily, and diclofenac group was received diclofenac SR 100mg once daily and diclofenac SR shaped placebo twice daily and SKI306X shaped placebo three times daily. Non-pharmacological managements such as massage therapy and exercise remained unchanged. Concomitant pharmacotherapies for conditions unrelated to OA were permitted if it is known not to significantly interact with either of the study medications. Oral corticosteroids, intra-articular steroid injection, acetaminophen, anticoagulants, H-2 blockers, antacids, and

other NSAIDs were prohibited during the trial.

Assessment of Efficacy and Safety

The primary efficacy variable was a change in the visual analogue scale (VAS) from baseline to the fourth week. Pain scores were given by patients using a horizontal 100mm score instrument labeled with "no pain" at the far left and "worst pain imaginable" on the right (Amundsen T *et al.*, 1983). Scores were obtained at baseline, the second week, and the fourth week. Secondary efficacy variables included i) Lequesne index consisting of 11 physician-administered questions about knee pain, walking distance, activities of daily living (Lund B *et al.*, 1998), ii) patients' global satisfaction score using 5-point scale (5=completely effective, 4=moderately effective, 3=mildly effective, 2=no change, and 1=worse), iii) investigators' global satisfaction score using 5-point scale same as the patients' score based on change of joint effusion, patellar tenderness, joint tenderness, pain on flexion, and active range of motion from baseline to 4th week visit.

Spontaneously reported adverse events and vital signs were recorded during each clinic visit Laboratory investigations, including hematology, chemistry, and urinalysis were performed at screening and 4th week.

For all adverse events, the investigators assessed causality between the adverse events and decided the degree of causality as follows: "definitely", "possibly and "probably" related

were scored as "drug-related" adverse events. Causality assessment has been done during the study period before breaking the code of blindness. Patients' compliance was assessed by counting the amount of returned study drugs at the 2nd- and 4th-week visits.

Statistical Analysis

Efficacy analysis was conducted on the intent-to-treat (ITT) population, defined as all randomized patients who satisfied both inclusion and exclusion criteria. The last-observation-carried-forward technique allowed the last treatment values recorded for patients who withdrew from the study prematurely to be reported as the final values. The student t-test was used to compare the study group's mean age, weight, height, baseline pain score and duration of OA. Chi-square test was used to test the difference in categorical variables between treatment groups. Overall efficacy of pain relief, as evaluated using VAS, was compared at baseline and the completion of 4-week treatment. Change of scores in VAS was computed as end score minus baseline score, so that positive change scores denote deterioration and negative scores improvement. Paired t-test was used to test the change of VAS score from baseline to the fourth week in each group. After reviewing the relevant literatures on the efficacy trials of NSAIDs, we determined that the pre-defined criterion for non-inferiority was less than 5mm difference of change in VAS score between two groups (Jung YB *et al.*, 2001). SKI306X would be considered clinically

not inferior to diclofenac if the lower limit of the 95% confidence interval (CI) does not extend beyond the predefined bound of –5 mm on the VAS. The analysis of covariance (ANCOVA) model allowed assessment of the pain score after treatment, as a function of the baseline pain score, treatment group, investigational site, sex, and age. The global satisfaction score given by patients and investigators were evaluated using the chi-square test.

The subjects of safety analysis consisted of a population of all treated patients among all randomized subjects. We evaluated the incidence of adverse events during the study and its 95% confidence intervals, its relationship to drugs and severity of the adverse event.

Sample Size

This study was designed as an equivalence trial with significance level 0.05 and with an 80% power for rejecting non-equivalence if the mean change in 100mm VAS scores before and after treatment differed by – 5 mm, assuming the standard deviation of change scores within groups was 15.0 mm. Our clinical experts panel selected –5 mm non-equivalence criterion based on literatures (Bellamy N *et al.*, 1993; Chow SC et al., 1992; Kirchheiner B *et al.*, 1976) and our phase II clinical study (Jung YB *et al.*, 2001). This power requirement led to a sample size of 112 per each treatment group

Preparation and Composition of SKI306X

SKI306X was prepared from the extracts of three medical herbs, Clematis Radix, Trichosanthes Root and Prunella Spike These extracts were combined at a 1:2:1 (w/w) ratio with 30% (v/v) ethanol-water. After the extracted solution was filtered and evaporated *in vacuo*, the residue was partitioned between *n*-butanol and water. The *n*-butanol layer was evaporated *in vacuo* and freeze-dried for complete removal of the residual solvent, yielding the final product in powder form. SKI306X was standardized according to the regulations imposed by Korean Food and Drug Administration. The active ingredients in SKI306X are oleanolic acid glycosides from Clematis Radix, rosmarinic acid and ursolic acid from Prunella Spike, and 4-hydroxybenzoic acid and *trans*-cinnamic acid from Trichosanthes Root. The 200 mg of SKI306X tablets also included general additives manufactured by a pharmaceutical company (SK Pharma Co. Ltd., Seoul, Korea).

RESULTS

Characteristics and Disposition of Patients

Between February 28, 2000 and August 28, 2000, a total of 249 patients were randomly assigned to one of two study groups: 125 subjects in the SKI306X group (male

9, female 116; age, 60.1 ± 8.1 years [mean ±SD]; baseline VAS score, 66.81 ± 15.4 [mean ±SD]) and 124 subjects in the diclofenac group (male 9, female 115; age, 59.7 ± 6.9 years; baseline VAS score, 65.28 ± 16.5) at 5 major university affiliated hospitals in South Korea. Baseline patient demographic and clinical characteristics of the two groups were well matched and no significant differences were observed. Two hundred fourteen out of the 249 total subjects (85.9%) completed four weeks of treatment. Withdrawal during the study included 20 out of 125 patients (16 %) in the SKI306X group and 15 out of 124 patients (12.1 %) in the diclofenac group. Most common reason for withdrawal was adverse events; 7/125 (5.6%) patients in the SKI306X group and 7/124 (5.6%) patients in the diclofenac group withdrew due to the experience of one or more adverse events. Reasons for withdrawal were evenly distributed among treatment groups (Table I)

[Table I around here]

Of the 249 patients enrolled, 248 patients were included in the intent-to-treat analysis. One patient in diclofenac group was excluded because we found that the patient failed to meet the entry criterion that the patient should have moderate pain greater than 35mm in VAS at the time of entry.

Efficacy

The mean (±SD) change in the VAS global pain score between the baseline and fourth week visit was –14.18 (±17.53) mm in the SKI306X group and –15.49 (±15 37) mm in the diclofenac group. The difference of mean change between the two groups was –1.31 mm with a 95% confidence interval of -4.75 to 2.13 mm (p=0.53, student t-test). The lower one-sided limit of this 95% confidence interval did not extend beyond the –5 mm range defined as the non-equivalence criterion, as detailed above in the "Materials and Methods" section.

Further analysis of the final VAS score was conducted using an analysis of covariance (ANCOVA). The covariates included the baseline pain score, treatment group, investigational site, sex and age. After adjusting for these covariates, there was no significant difference in pain relief between the two groups (p=0.50, ANCOVA test).

The analysis of Lequesne index from baseline to the fourth week indicated that there was significant difference between the two groups (mean±SD): -1.95 (±2.77) in SKI306X group (baseline 12.21±4.18, 4th week 10 26±4.80) vs. –2.72 (±2.62) in diclofenac group (baseline 11.86±3.30, 4th week 9 14±3.79) (p = 0.03, student t-test) and both groups had significant changes with time (p = 0.0, paired t-test).

The global satisfaction assessment by the investigators and patients at the fourth week

did not show any significant difference between two groups. Mantel-Haenszel Chi-Square test was used for patients' trend test, but Q_{MH} was 2.07 and p-value was 0.15. Therefore the difference between the number of moderately effective patients and mildly effective patients was not statistically significant (Table II).

[Table II around here]

Safety and Tolerability

Throughout the study, there was no significant difference in the incidence of adverse events between treatment groups (29.6% of patients in the SKI306X and 34.7% in the diclofenac group, p=0.390, chi-square test). Drug-related adverse events were significantly less frequent in SKI306X (22/125, 17.6.%) than in the diclofenac group (36/124, 29.%) (p=0.033, chi-square test) even though both SKI306X and diclofenac in general were well tolerated. Three of the 44 (6.8%) events reported in the SKI306X treatment group were rated as severe according to the protocol-defined reporting criteria, while 11 of the 61 events (18.0%) were rated as severe in the diclofenac group (data not shown). In the diclofenac group, one life-threatening serious adverse event of intracranial hemorrhage was reported in a patient with hypertension; however, this event was considered unrelated to the drug by the investigator.

[Table III & IV around here]

Adverse events most commonly reported in both groups involved the gastrointestinal system, which accounted for 22.4% of the adverse events in the SKI306X group and 25.8% in the diclofenac group (Table III). The majority of clinical adverse events affected the digestive system, accounting for 52.5%(32/61) to 63.6%(28/44) of all events in both treatment groups. In special among the digestive system adverse events the single most common drug-related clinical adverse event was heartburn, which was observed in 3 patients (4.05%) in SKI306X group and 17 patients (13.7%) in the diclofenac group (p=0.021, chi-square test)(data not shown)

Table IV shows the result of laboratory measurements, in which the numbers represent the number of patients who had normal laboratory values at baseline and ended with abnormal values at the completion of the study. Elevations of ALT in diclofenac SR were more frequent than that in SKI 306X group (2 vs.11), which was statistically significant difference (p=0.01). And also with regard to aspartate aminotransferase (AST), there is more frequent elevation in diclofenac group than in SKI 306X group, although there is no statistically significant difference (p=0.10). Regarding vital signs including heart rate and blood pressure, there were no clinically or statistically significant changes in time for either treatment.

DISCUSSION

The efficacy and safety of SKI306X in treatment of OA of the knee was previously studied in a randomized, double blind, placebo-controlled study (Jung YB *et al.*, 2001). The main goal of this study was to compare the efficacy and safety of a SKI306X with diclofenac SR, a NSAID with proven efficacy and safety for the treatment of OA of the knee. The results of this study indicated that the efficacy of SKI306X 200 mg three times a day is comparable to that of diclofenac SR 100 mg a day. Most of all, improvement of primary efficacy variable, VAS, was not significantly different between two groups. This conclusion was supported by the analysis of other secondary efficacy measures such as patients' and investigators' global satisfaction assessment score. However, diclofenac did appear to be more efficacious based on the results of the Lequesne index only. In the diclofenac group, there were a greater number of total adverse events than in the SKI306X group, largely due to the greater incidence of increased serum ALT and AST levels in the former group.

This study was conducted as a well-designed, randomized, multicenter, double blind study and blinding was maintained by using double dummy technique, which could reduce the chance of introducing information bias on evaluating the efficacy with highly

subjective outcome criteria such as VAS. The Clinical Trial Center at Seoul National University Hospital has been played a role as a coordinating center for handling all study related problems such as randomization, collecting CRF and standardization of study process. In order to assure the quality of data management process, we used software of clinical data management system, ClinTrial 4®, which was specifically designed for managing data from clinical trials.

However, the results of primary efficacy variable VAS did not correspond to the results of secondary efficacy variables Lequesne index might be the limitation of this study. Further study to evaluate this problem will be needed. And, this short treatment is not sufficient to fully reveal the beneficial and adverse effects of SKI306X, there is a clear need to evaluate SKI306X for a longer treatment period. If the long-term study reveals that its efficacy is comparable to that of the other existing NSAIDs and its safety is better than that of the standard NSAIDs therapy, SKI 306X will be regarded as the drug of choice for treating the OA patients.

In conclusion, this study showed that SKI306X 200 mg three times daily has similar clinical efficacy, yet superior safety and tolerability, for treating OA of the knee, as compared to diclofenac SR 100 mg once daily during a four-week treatment period.

ACKNOWLEDGEMENTS

This clinical study was partially supported by the Ministry of Health and Welfare of Korea (HMP-98 D-7-0014), and Life Science Research Center of SK Chemicals, Korea.

The authors acknowledge the collaboration and commitment of all of the investigators and people concerned without whom the present study would not have been possible. Sang-Un Park and Chang-Joo Hwang of Seoul National University; Won-Hwan Oh of Sungkyunkwan University; Chung-Ho Cho of Ewha Woman's University; Jung-Tae Suh and Jung-Ho Chang of the Catholic University of Korea; Jin-A Jung, Ki-Won Jung, Ji-Young Lee, Myung-Ju Byun, Ji-Hwa Ryu, Ji-Hae Kim, Eun-Kyoung Kim, Jin-Sil Park and Sung-Min Lee of Life Science Research Center of SK Chemicals, Korea.

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Table I. Disposition of study subjects and reasons for discontinuation

Disposition status	SKI306X	Diclofenac	Total
	N (%)	N (%)	N (%)
Patients randomized	125	124	249
Completed treatment	105 (84.0)	109 (87.9)	214 (85.9)
Failure to meet inclusion criteria*	0	1	1
Discontinued treatment	20 (16.0)	15 (12.1)	35 (14.1)
Clinical adverse experience	7 (35.0)	7 (46.7)	14 (40.0)
Lack of efficacy	1 (5.0)	1 (6.7)	2 (5.7)
Protocol violation	1 (5.0)	0 (0.0)	1 (2.9)
Lost to follow-up	7 (35.0)	4 (26.7)	11 (31.4)
Patient withdraw	4 (20.0)	3 (20.0)	7 (20.0)

* One patient in diclofenac group failed to meet the inclusion criteria..

Table II. Comparison of the global satisfaction assessments by the investigators and patients at 4 weeks of treatment

Assessment	SKI306X N (%)		Diclofenac N (%)		p-value	
	Investigators	Patients	Investigators	Patients	Investigators	Patients
Completely effective	42 (35.6)	9 (7.6)	42 (35.0)	9 (7.6)	0.93[1)]	0.26[1)]
Moderately effective	18 (15.3)	30 (25.4)	20 (16.7)	43 (36.1)		0.15[2)]
Mildly effective	27 (22.9)	48 (40.7)	29 (24.2)	40 (33.6)		
No change	24 (20.3)	23 (19.5)	21 (17.5)	24 (20.2)		
Worse	7 (5.9)	8 (6.8)	8 (6.7)	3 (2.5)		
Total	118 (100.0)	118 (100.0)	120 (100.0)	119(100.0)		

1) p-value by Chi-square test
2) p-value by Mantel-Haenszel Chi-Square test

Table III. Comparison of incidence of adverse events by body system and drug relatedness

Body system [1]	SKI306X (N=125)	Diclofenac (Total N=124)	Total (N=249)
	N (%)	N (%)	N (%)
Allergy	0 (0.0)	1 (0.8)	1 (0.4)
Cardiovascular	3 (2.4)	3 (2.4)	6 (2.4)
Dermatological	2 (1.6)	0 (0.0)	2 (0.8)
Digestive	28 (22.4)	32 (25.8)	60 (24.1)
Musculoskeletal	0 (0.0)	1 (0.8)	1 (0.4)
Neurological	1 (0.8)	5 (4.0)	6 (2.4)
Respiratory	6 (4.8)	2 (1.6)	8 (3.2)
Renal/Genitourinary	1 (0.8)	5 (4.0)	6 (2.4)
Others	3 (2.4)	12 (9.7)	15 (6.0)
Total number of AE* [2]	44 (35.2)	61 (49.2)	105 (42.2)
Total number of patients experiencing AE [3]	37 (29.6)	43 (34.7)	80 (32.1)
Total number of drug related AE [2]	24 (19.2)	46 (37.1)	70 (28.1)
Total number of patients experiencing drug related AE [4]	22 (17.6)	36 (29.0)	58 (23.3)
Total number of patients with serious AE	0 (0.0)	1 (0.8)	1 (0.4)

[1] COSTART Classification of Adverse Events, [2] Some patients had more than one Adverse Events, [3] p-value was 0.390 by chi-square test; [4] p-value was 0.033 by chi-square test

*AE = adverse events

Table IV. Patients with abnormal laboratory values at study conclusion

Laboratory Measurements	SKI306X (N=125)	Diclofenac (Total N=124)	Total (N=249)	p-value[1)]
	N (%)	N (%)	N (%)	
Chemistry				
Glucose	14 (11.2)	16 (12.9)	30 (12.1)	0 68
BUN	9 (7.2)	13 (10 5)	22 (8.8)	0 36
Creatinine	5 (4 0)	3 (2.4)	8 (3.2)	0.72
Protein, total	5 (4.0)	4 (3.2)	9 (3 6)	1.00
Albumin	1 (0 8)	0 (0.0)	1 (0 4)	1.00
Bilirubin, total	2 (1 6)	1 (0.8)	3 (1 2)	1 00
Alkaline phosphatase	2 (1 6)	2 (1.6)	4 (1.6)	1 00
ALT	2 (1 6)	11 (8.9)	13 (5.2)	0 01
AST	2 (1 6)	7 (5.7)	9 (3.6)	0 10
GGT	2 (1 6)	6 (4.8)	8 (3 2)	0 17
Hematology				
WBC	5(4.0)	5(4 0)	10(4 0)	1 00
RBC	6(4.8)	11(8.9)	17(6 8)	0.20
Hemoglobin	2(1 6)	6(4.8)	8(3.2)	0 17
Hematocrit	5(4 0)	11(8.9)	16(6.4)	0 12

[1)] p-value by chi-square test or Fisher's exact test